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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

ROBERTS, LEZAH

ART UNIT

PAPER NUMBER

1612

MAIL DATE

DELIVERY MODE

06/09/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary**Application No.**

10/728,277

Applicant(s)

ROSENTHAL ET AL.

Examiner

LEZAH W. ROBERTS

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 March 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 17, 19, 20, 24, 25, 31, 35, 38, 133-136, 142, 145 and 148-152 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 17, 19, 20, 24, 25, 31, 35, 38, 133-136, 142, 145 and 148-152 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-840)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Applicants' arguments, filed March 2, 2010, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims

Claim Rejections - 35 USC § 103 – Obviousness

1) Claims 1, 17, 19, 20, 24, 25, 31, 38, 133-136, 142, 145 and 148-152 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeck et al. (US 6,620,428) in view of Krezanoski (US 4,188,373) and Osol ed. (Remington's Pharmaceutical Sciences, 1980).

Applicant's Arguments

Applicant argues Krezanoski is not analogous art with respect to either Hoeck et al. or Osol; one of ordinary skill would not find obvious a combination of the teachings of Hoeck et al, Krezanoski and Osol as proposed by the Examiner; and there is persuasive objective evidence of nonobviousness in relation to significant and unexpected

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properties of the claimed composition as effective for treatment of oral mucositis as a side effect of cancer therapy and in relation to a long felt unsolved need addressed by the claimed composition-for such a treatment. Hoeck et al., Krezanoski nor Osol are concerned with a treatment of oral mucositis. Hoeck et al. focuses on transdermal delivery of N-acetyl cysteine as a mucolytic agent, or expectorant, which is significantly different than and not indicative of efficacy for treatment of mucositis, as discussed in the Troha Declaration. Although Krezanoski states that "any pharmaceutically active material" may be included in the disclosed drug delivery composition, the disclosure of Krezanoski is clearly directed to delivering drugs to a mucous membrane, primarily to ocular pharmaceutical applications. Applicant further argues that for temporary transmucosal delivery, Hoeck et al. disclose using the same forms of administration as disclosed for transdermal delivery. Moreover, the teachings by Hoeck et al. are teaching away from combining N-acetyl cysteine with delivery compositions targeted to mucosal delivery, such as the delivery composition of Krezanoski. Krezanoski teaches away from using a transmucosal delivery as disclosed by Hoeck because increased mucosal absorption of drug and prolonged response from transmucosal delivery would logically interfere with the desired transdermal delivery of N-acetyl cysteine as taught by Hoeck et al.

Applicant further argues, assuming *arguendo* that one of ordinary skill in the art would for some reason be motivated to look beyond Hoeck et al. for other possible compositions for transmucosal delivery for the short duration by Hoeck et al., there would be a multitude of possibilities of which the teachings of Krezanoski would be only

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one, and in that regard, this situation seems to be particularly susceptible to hindsight biases. Prior art such as Dobrozsi et al. and Ron et al. teach away from the use of drug delivery compositions of the very type disclosed by Krezanoski for mucosal drug delivery. Considering the prior art as a whole, one would not be led to a combination of Hoeck et al. with Krezanoski as asserted by the Examiner.

Applicant further argues that assuming *arguendo* that the Examiner did make a *prima facie* showing of obviousness based on Hoeck et al. and Krezanoski, the application specification and the Troha Declaration provide significant evidence of a long-felt but unsolved need for a treatment for oral mucositis as a side effect of cancer therapy. The Declaration also shows the A2.02/RK-0202 composition formulated with both the N- acetyl cysteine and the poloxamer 407 significantly outperformed the other compositions, including the A2.03/RK-0203 composition that contained the N-acetyl cysteine in water without the poloxamer 407. There are significant differences between the A2.02/RK-0202 composition and the A2.03/RK- 0203 composition. The results in the Declaration would not be expected due simply to the change in delivery vehicle (from the formulation without to the formulation with the poloxamer 407). Also, the vehicle control and water control compositions performed significantly worse than either of the formulations containing N- acetyl cysteine. Therefore, evidence presented in the application specification and the Troha Declaration show that the claimed composition has a property, unexpected from the prior art, of being particularly effective for treatment of oral mucositis as a side effect of cancer therapy, and that the claimed composition addresses a long-felt but unsolved need for such a treatment.

Applicant argues the Examiner uses hindsight in regard to analyzing the Troha Declaration. The limited disclosure by Krezanoski is insufficient to support a broad application of the teachings of Krezanoski that essentially any drug that may ever have been administered mucosally for any purpose would be "expected" to have obviously enhanced performance when formulated in the delivery vehicle of Krezanoski. The Examiner gave insufficient weight to evidence of secondary considerations in the Troha Declaration of unexpected properties, e.g., significant and unexpected efficacy for treatment of oral mucositis.

Examiner's Response

Hoeck et al. suggest using a transmucosal composition initially in conjunction with the transdermal patch taught by Hoeck. This transmucosal route may be oral, sublingual, buccal, nasal, pulmonary and rectal, or possibly other transmucosal. These types of transmucosal administration routes of N-acetyl-L-cysteine result in the drug reaching the system more rapidly than through the disclosed transdermal route. Krezanoski discloses that the vehicles comprising poloxamer result in improving drug delivery through the mucous membranes, which would include the oral cavity. The vehicles hold the medicament in place for a long period of time. This would not appear to teach away from Hoeck et al because the drug would be able to be delivered at suitable concentrations and long enough for the transdermal patch of Hoeck et al to take effect. The vehicle also increases the pharmacological response and therefore

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would result in the drug reaching the system more rapidly. In regard to the vehicles of Krezanoski being for ocular applications, the vehicles are also suitable of use in the oral cavity as evident by Piechota Jr., cited below. Even if this were not the case, Hoeck et al. disclose other transdermal routes, which it is reasonable to conclude, may also include the mucosa of the eye. In regard to the references not disclosing mucositis, the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See MPEP 2144, IV. Thus the combination of references does not have to disclose or provide motivation for making a composition for treating mucositis. The combination does, however, provide the motivation for making a composition comprising the poloxamer and N-acetyl cysteine as a mucolytic/expectorant composition wherein N-acetyl cysteine is used in a concentration effective as a mucolytic/expectorant.

In regard to Applicant's assertion that Krezanoski discloses making the transmucosal formulations using the same forms of administration as disclosed for transdermal delivery, the reference discloses:

One suitable use of the mentioned forms of administration is to administer N-Acetyl-L-cysteine through the oral, sublingual, buccal, nasal, pulmonary and rectal, or possibly other transmucosal, route at approximately the same time as the first transdermal device is applied. Thereafter new transdermal devices are applied to ensure the correct plasma level without further administration through the oral, sublingual, buccal, nasal, pulmonary and rectal, or possibly other transmucosal, routes. The above concomitant use of different administration forms is especially useful in certain situations, such as, but not exclusively, some time prior to oral presentations, attendance to conferences and visits to theatres, concerts and church. It is thus feasible to market set of formulations including devices for transdermal administration as well as devices or formulations for oral, sublingual, buccal, nasal, rectal, pulmonary

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and rectal, and possibly other transmucosal, administration of N-Acetyl-L-cysteine.

No where does the reference disclose that the different routes of administration have to be in the same form as the transdermal composition, only that they are packaged together. The reference also discloses "devices or formulation" which would include forms other than those disclosed by Hoeck. Thus it is reasonable for one of ordinary skill in the art to look to the prior art, such as Krezanoski, to find forms suitable for transmucosal administration.

Although there are prior art references that teach the disadvantages of using the vehicles of Krezanoski, such as Dobrozsi et al and Ron et al (discussed by Applicant), there are also prior art references that disclose using vehicles similar to Krezanoski. These include Viegas et al (USP 5,593,683), which refer to the vehicles of Krezanoski and disclose compositions comprising the poloxamers of Krezanoski in concentrations, which also overlap those of the instant claims. Trom et al. (USP 6,669,927) also disclose using the poloxamers of Krezanoski in similar concentrations in their disclosed oral compositions (see Tables). Thus it would appear looking at the prior art as a whole that one of ordinary skill in the art would not be deterred from using the vehicles of Krezanoski based on the disclosures of Dobrozsi et al and Ron et al. Further in the case of Ron, Ron discloses that the compositions of Krezanoski are viscous and may cause unfavorable physiological interactions during use. This does not necessarily mean that it will cause unfavorable interactions and having a viscous vehicle for use in formulating transmucosal formulations would appear beneficial because this would lead to the

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composition staying in the desired location longer than a less viscous solution and would therefore promote the delivery of the drug through the mucosa. In the case of Dobrozsi et al., the reference also discloses that vehicles similar to Krezanoski are commonly used and are used for oral preparations. Thus is reasonable to conclude that one of ordinary skill in the art would use a vehicle commonly used to formulate the transmucosal compositions of Hoeck et al.

In regard to the alleged unexpected result, it is agreed that N-acetyl cysteine is effective for treating mucositis. Based on the evidence provided, this would appear to be the case whether the active was in water or some other mucoadhesive vehicle. It does not appear to be unexpected that N-acetyl cysteine in a poloxamer vehicle is more effective than one in water because the poloxamer vehicle has a longer residence time than water and would therefore leave the active in contact with desired point of delivery longer making the composition more effective. This is supported by Krezanoski as well as Piechota Jr. below. It is further argued that the vehicle control performed worse than that of the both N-acetyl cysteine samples. This appears not to be the case through day 12 where the vehicle actually performed better than RK-0203. It cannot, however, be determined if this is due to the chitosan in the vehicle or the poloxamer.

Although the references do not teach mucositis, they do provide motivation for formulating a composition comprising N-acetyl cysteine and poloxamer 407. As stated above, the results do not appear to be unexpected because the prior art teaches that vehicles such as those disclosed by Krezanoski increase the bioavailability of a drug

and would therefore increase its effectiveness. Thus, based on the teachings in the prior art, hindsight reasoning was not used.

2) Claims 1, 17, 19, 20, 24, 25, 31, 35, 133-136, 142, 145 and 148-152 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeck et al. (US 6,620,428) in view of Piechota, Jr. (US 5,256,396) and Osol ed. (Remington's Pharmaceutical Sciences, 1980).

Applicant's Arguments

Applicant argues Piechota is not analogous art with respect to either Hoeck et al. or Osol; one of ordinary skill in the art would not find the combination of references obvious; and there is objective evidence of nonobviousness. The arguments in regard to Piechota are similar to those in regard to Krezanoski et al above.

Examiner's Response

In regard to the Piechota not being analogous art, the reference teaches oral compositions and Hoeck et al. suggest transmucosal formulations for buccal, oral or possibly other transmucosal administration of N-acetyl-L-cysteine which results in the drug reaching the system more rapidly than through the transdermal route. Thus Piechota is analogous to the teachings of Hoeck et al. Hoeck et al. specifically teaches that a second route of administration of N-acetyl-L-cysteine along with the transdermal route is of value. A second route that results in the drug reaching the system more

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rapidly is strongly suggested. Piechota discloses a vehicle that enhances the delivery of actives to the oral cavity and thus one would be motivated to use the vehicles to deliver the mucolytic agent of Hoeck et al., even if the compositions are used as initial compositions or as compositions used in conjunction of a transdermal composition. In regard to Osol, Osol discloses that N-acetyl cysteine is formulated into 10% or 20% solutions and thus one of ordinary skill in the art would use these doses to formulate the compositions of the combined teachings of Hoeck et al. and Piechota. In regard to the references not disclosing mucositis, the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See MPEP 2144, IV. Thus the combination of references does not have to disclose or provide motivation for making a composition for treating mucositis. It does however provide motivation for making a composition comprising N-acetyl cysteine and a poloxamer as a mucolytic/expectorant composition.

See Examiner's response above in regard to the prior art as a whole, including the discussion of one of skill in the art looking to other delivery formulations and the teaching away of Dobrozsi et al. and Ron et al. from compositions disclosed by Piechota. In regard to Applicant's objective evidence of nonobviousness, see Examiner's Response above.

Obvious-Type Double Patenting

1) Claims 1, 17, 19, 20, 24, 25, 31, 35, 38, 133-136, 142, 145 and 148-152 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5, 6 and 8-23 of U.S. Patent No. 6,685,917. Claims 13, 15, 137, 140, 143, 146 and 147 are cancelled.

Applicant will file appropriate terminal disclaimers upon indication of allowable subject matter.

2) Claims 1, 17, 19, 20, 24, 25, 31, 35, 38, 133-136, 142, 145 and 148-152 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5, 6 and 8-23 of U.S. Patent No. 6,685,917 in view of Krezanoski (US 4,188,373).

Applicant will file appropriate terminal disclaimers upon indication of allowable subject matter.

3) Claims 1, 17, 19, 20, 24, 25, 31, 35, 38, 133-136, 142, 145, and 148-152 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of copending Application No. 11/605,983.

Applicant will file appropriate terminal disclaimers upon indication of allowable subject matter.

The copending application 11/605,983 is now USP 7,501,452. Thus the rejection is no longer a provisional rejection. The claims now stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23

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of US Patent No. 7,501,452 over the same grounds as asserted in the Office Action mailed January 8, 2009.

Claims 1, 17, 19, 20, 24, 25, 31, 35, 38, 133-136, 142, 145 and 148-152 are rejected.

No claims allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to LEZAH W. ROBERTS whose telephone number is (571)272-1071. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lezah W Roberts/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612